UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte WALTER HENRY GUNZBURG and ROBERT MICHAEL SALLER

Appeal No. 2006-2597
Application No. 08/808,827

ON BRIEF

Before GRIMES, LINCK, and LEBOVITZ, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

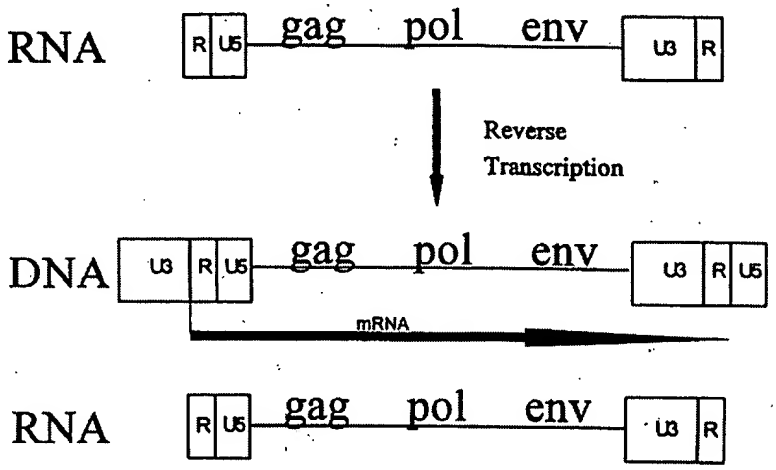
DECISION ON APPEAL

This appeal involves claims to retroviral vectors, which the examiner has rejected as obvious. We have jurisdiction under 35 U.S.C. § 134. We reverse.

Background

The specification discloses a "retroviral vector which can be used as a safe gene transfer vehicle for targeted gene therapy. This novel vector carries heterologous promoter and/or regulatory elements in the 3'LTR which, after infection[,] become duplicated and translocated to the 5'LTR in the target cell, eventually controlling expression of marker/therapeutic genes . . . inserted into the body of the vector." Pages 9-10.

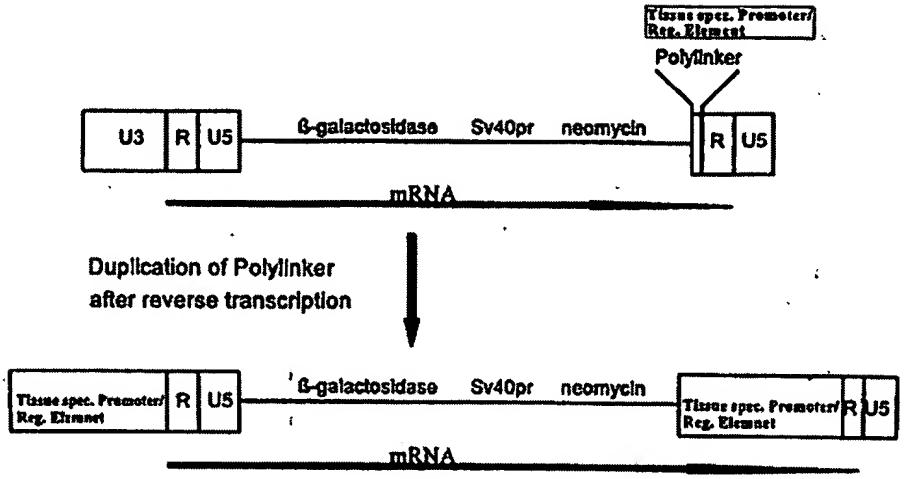
"The retroviral genome consists of an RNA molecule with the structure R-U5-gag-pol-env-U3-R (Fig. 2)." Specification, page 14. Figure 2 is shown below:



The figure is said to illustrate the effect of reverse transcription on retroviral structure: "During the process of reverse transcription, the U5 region is duplicated and placed at the right hand end of the generated DNA molecule, while the U3 region is duplicated and placed at the left hand end of the generated DNA molecule. . . . The resulting structure U3-R-U5 is called LTR (Long Terminal Repeat) and is thus identical and repeated at both ends of the DNA structure or provirus." Specification, page 14.

"The U3 region at the left hand end of the provirus harbors the promoter. . . . This promoter drives the synthesis of an RNA transcript initiating at the boundary between the left hand U3 and R regions and terminating at the boundary between the right hand R and U5 regions (Fig. 2). This RNA is packaged into retroviral particles and transported into the target cell." Id.

In the retroviral vector disclosed in the specification, "the right-hand U3 region is altered (Fig. 3), but the normal left-hand U3 structure is maintained." Pages 14-15. The relevant part of Figure 3 is shown below:



The figure shows a retroviral vector in which the right-hand U3 region is replaced with a polylinker, into which a heterologous promoter is inserted. The specification explains that "the vector can be normally transcribed into RNA utilizing the normal retroviral promoter located within the left-hand U3 region (Fig. 3). However[,] the generated RNA will only contain the altered right-hand U3 structure. In the infected target cell, after reverse transcription, this altered U3 structure will be placed at both ends of the retroviral structure." Page 15. The heterologous "promoter will then be utilized exclusively in the target cell for expression of linked genes carried by the retroviral vector," such as the β-galactosidase gene shown in Figure 3. Id.

"[B]oth LTRs will consist to a large extent of heterologous promoter/enhancer sequences in the target cell. This . . . will reduce the chance of recombination with endogenous retroviral sequences to generate potentially pathogenic replication competent virus, increasing the safety of the system." Specification, page 10.

Discussion

1. Claims

Claims 1, 5, 7, 9-26, 28, 29, and 31-78 are pending and on appeal. Claim 1 is representative and reads as follows:

1. A retroviral vector which undergoes promoter conversion comprising in 5' to 3' order,

   (a) a 5' long terminal repeat region of the structure U3-R-U5;

   (b) one or more coding sequences, said sequences being inserted into the body of the vector; and

   (c) a 3' long terminal repeat region comprising a partially deleted U3 region into which a polylinker sequence containing a heterologous promoter has been inserted,

   wherein after infection of a target cell, said U3 of said 5' long terminal repeat region is replaced by said partially deleted U3 region and said heterologous promoter, resulting in said one or more coding sequences becoming operatively linked to said heterologous promoter and said heterologous promoter regulating expression of said one or more coding sequences in said target cell.

Claim 1 defines a retroviral vector having a left-hand (5') LTR with the usual U3-R-U5 structure, a coding sequence inserted into the body of the vector (i.e., between the LTRs), and a right-hand (3') LTR "comprising a partially deleted U3 region into which a polylinker sequence containing a heterologous promoter has been inserted."

The specification states that "[t]he term 'heterologous' is used for any combination of DNA sequences that is not normally found intimately associated in nature." Page 15, lines 21-24. "[T]he term 'polylinker' is used for a short stretch of artificially synthesized DNA which carries a number of unique restriction sites allowing the easy insertion of any promoter." Page 15, lines 18-21. "Said polylinker sequence carries at least one unique restriction site." Page 11, lines 12-13.

The specification does not expressly define the term "partially deleted U3 region." A "partially deleted" region, however, must be missing some of the region that would normally be present. In addition, the specification distinguishes between "partially" and "completely" deleted. See, e.g., page 11, line 9 ("completely or partially deleted U3 region") and original claim 1 ("3' long terminal repeat region comprising a completely or partially deleted U3 region"). Since the claims have been limited to vectors comprising a "partially deleted" U3 region, we interpret claim 1 to exclude vectors having a completely deleted U3 region. That is, the claimed vector is missing part, but not all, of the U3 region in the 3' LTR.

"[T]he PTO applies to the verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in the applicant's specification." In re Morris, 127 F.3d 1048, 1054, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997).

Giving claim 1 its broadest reasonable interpretation consistent with the specification, we interpret it as follows: the claimed vector is missing part, but not all, of the U3 region in the 3' LTR; the U3 region of the 3' LTR includes a "short stretch of artificially synthesized DNA" that includes at least one restriction site that is unique with respect to the rest of the vector; and a promoter has been inserted into the non-naturally occurring DNA, the promoter being one that is not naturally a part of the retrovirus from which the vector is derived (i.e., a heterologous promoter).

Claim 1 also includes a "wherein" clause that describes how the vector functions: after infection of a target cell, the 3' U3 region with its heterologous promoter is duplicated on the 5' end of the provirus, resulting in the coding sequence "becoming operatively linked to said heterologous promoter and said heterologous promoter regulating expression of said one or more coding sequences in said target cell."

2. Obviousness

The examiner rejected all of the pending claims under 35 U.S.C. § 103 as obvious in view of the prior art, as follows:

• Claims 1, 5, 9, 11, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 65-72, and 74-78 as obvious in view of Couture[1] and Faustinella;[2]

• Claims 1, 5, 7, 9, 11, 16-25, 28, 29, 31, 32, 56-59, 61, 65-72, and 74-78 as obvious in view of Couture, Faustinella, and Mee;[3]

• Claims 1, 5, 7, 9, 11, 15-25, 28, 29, 31-36, 38, 42-49, and 51-55 as obvious in view of Couture, Faustinella, and Mehigh;[4]

• Claims 1, 13, 14, 33, 40, 41, 56, 63, and 64 as obvious in view of Couture and Faustinella (optionally combined with Mee and/or Mehigh), Miller,[5] and Panganiban;[6]

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[1] Couture et al., "Retroviral vectors containing chimeric promoter/enhancer elements exhibit cell-type-specific gene expression," Human Gene Therapy, Vol. 5, pp. 667-677 (1994).
[2] Faustinella et al., "A new family of murine retroviral vectors with extended multiple cloning sites for gene insertion," Human Gene Therapy, Vol. 5, pp. 307-312 (1994).
[3] Mee et al., "Construction and hormone regulation of a novel retroviral vector," Gene, Vol. 88, pp. 289-292 (1990).
[4] Mehigh et al., "Development of a recombinant bovine leukemia virus vector for delivery of a synthetic bovine growth hormone-releasing factor gene into bovine cells," J. Anim. Sci., Vol. 71, pp. 687-693 (1993).
[5] Miller et al., "Improved retroviral vectors for gene transfer and expression," Biotechniques, Vol. 7, pp. 980-990 (1989).
[6] Panganiban et al., "The retroviral pol gene encodes a product required for DNA integration: Identification of a retrovirus int locus," Proc. Natl. Acad. Sci. USA, Vol. 81, pp. 7885-7889 (1984).

• Claims 1, 10, 12, 33, 37, 39, 56, 60, and 62 as obvious in view of Couture and Faustinella (optionally combined with Mee and/or Mehigh), and Price;[7] and

• Claims 17, 20, 21, 26, 28, 43, 50-53, 66, and 73-76 as obvious in view of Couture and Faustinella (optionally combined with Mee and/or Mehigh), Longmore,[8] and Kay.[9]

Each of the examiner's rejections depends on the combination of Couture and Faustinella. The examiner noted that Couture teaches retroviral vectors meeting some of the limitations of the instant claims:

> Couture . . . shows retroviral vectors comprising a substitution of a portion of the 3' U3 region with the corresponding region of 5 different murine retroviruses. . . . [T]he inserted region comprises an enhancer regulatory element and a promoter. Couture et al. shows . . . that the first 40 nucleotides of the original vector are retained in the substitution of the U3 region. The vector of Couture comprises a chloramphenicol acetyl transferase marker gene.

Examiner's Answer, page 5. The examiner acknowledged that "Couture et al. does not show a vector comprising a multiple cloning site [i.e., a polylinker] in the U3 region." Id. He cited Faustinella as teaching this aspect of the claimed vector:

> Faustinella et al. shows in figure 1 Moloney murine leukemia retroviral vector pS3. pS3 comprises a partial deletion of the 3' U3 region, into which has been inserted a polylinker with unique cloning sites, for example the Bsa AI site and the Nae I site used to construct the vectors of figure 2.
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> It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the vectors of Couture et al. by adding the multiple cloning site of Faustinella et al. because Faustinella et

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[7] Price et al., "Lineage analysis in the vertebrate nervous system by retrovirus-mediated gene transfer," Proc. Natl. Acad. Sci. USA, Vol. 84, pp. 156-160 (1987).
[8] Longmore et al., "Both megakaryocytopoiesis and erythropoiesis are induced in mice infected with a retrovirus expressing an oncogenic erythropoietin receptor," Blood, Vol. 82, pp. 2386-2395 (1993).
[9] Kay et al., "In vivo gene therapy of hemophilia B: Sustained partial correction in Factor IX-deficient dogs," Science, Vol. 262, pp. 117-119 (1993).

> al. shows that multiple cloning sites may be used to insert sequences of choice in a U3 region of a retroviral vector.

Examiner's Answer, pages 5-6.

Appellants argue that "adding a polylinker to Couture's vector does not create a retroviral vector with a partially deleted U3 region as recited in claim 1." Appeal Brief, page 16. That is, "Couture did not simply substitute portions of the U3 regions from [different] viruses, but rather replaced the sequences with the exactly corresponding sequences from five highly related murine retroviruses . . . such that when the 'portions' were cloned into the deletion, a complete 3' LTR was produced." Id., page 17.

Appellants have provided a declaration by Christine Leib-Moesch to support their position.[10] Dr. Leib-Moesch declared that

> [t]he replacement strategies disclosed in Couture produce complete chimeric LTRs 'based on the substitution of the MoMLV U3 region with the U3 region from the murine retroviral isolates SL3-3, AKV, Xeno, HaMSV, and MPSV' (Couture at page 669). This was accomplished by employing conserved restriction sites present in the 3' LTR of these retroviruses.

¶ 5. Dr. Leib-Moesch concludes that "Couture teaches producing complete, although chimeric, 3' LTRs by 'swapping' corresponding regions of the 3' U3 sequences of five related retroviruses into the vector." ¶ 6.

The examiner argues (Examiner's Answer, page 12) that

> [t]he appellants equate the claimed partially deleted U3 region with an incomplete U3 regions, however this is not correct and claims 1, 17, 28, 56, [and] 66 do not require an incomplete or defective U3 region. Couture et al. first deleted a region of the original U3 region as required by claims 1, 17, 28, 56, [and] 66 and then inserted a substitute sequence that restored function to the 3' LTR consisting of an LTR sequence from a different murine leukemia retrovirus.

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[10] Declaration of Christine Leib-Moesch filed under 37 CFR § 1.132, received April 18, 2005. The examiner stated in the Advisory Action mailed May 26, 2005 that the declaration had been considered.

We agree with Appellants that claim 1 defines a vector that has a partially deleted U3 region; i.e., the vector is missing some but not all of the U3 region from the 3' LTR. The examiner argues that Couture's vectors meet this limitation because part of the original U3 region was deleted and replaced by the corresponding fragment from a different retrovirus.

The examiner, however, has not established that those skilled in the art would interpret the "U3 region" recited in the claims to require a naturally occurring U3 region. The examiner correctly notes that Couture's experiment included deleting part of the original (MoMLV) 3' U3 region of the starting vector. However, the examiner has not disputed Appellants' assertion that the missing part of the 3' U3 region was precisely replaced by the corresponding part of another retrovirus, resulting in "complete, although chimeric, 3' LTRs." See the Appeal Brief, page 18 (quoting the Leib-Moesch declaration).

The claims are directed to products, not methods of making the products. Claim 1 requires that the product have a U3 region that is "partially deleted." Therefore, in the claimed vector, the U3 region in the 3' LTR must be missing some of its constituent nucleotides; i.e., part of the structure must be not just different from a naturally occurring structure, but deleted.

The evidence of record shows that when Couture exchanged part of the MoMLV U3 region for the equivalent part of the U3 region from a different virus, the result was a vector with a complete U3 region – a chimeric, non-naturally occurring U3 region, but a complete U3 region nevertheless. Therefore, we agree with Appellants that even if Couture's vectors were modified by inserting a polylinker into the U3 region of the 3'

LTR, the resulting product would not meet all the limitations of claim 1 because it would not have a "partially deleted U3 region."

The examiner has not adequately explained how Couture and Faustinella would have suggested the product of claim 1. The rejection of claims 1, 5, 9, 11, 16-25, 28, 29, 31, 32, 56, 57, 59, 61, 65-72, and 74-78 as obvious in view of Couture and Faustinella is reversed.

In all of the other rejections on appeal, the examiner relies on the same reasoning discussed above, and cites additional references to meet limitations of dependent claims. The examiner has pointed to nothing in the additional references to teach or suggest retroviral vectors having a partial deletion of the U3 region in the 3' LTR, and no such teaching or suggestion is apparent to us. Therefore, all of the other rejections suffer the same deficiency as the rejection based on Couture and Faustinella, and must be reversed for the same reason.

REVERSED

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